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Leukaemia Section
Mini Review

t(7;9)(q11;p13)

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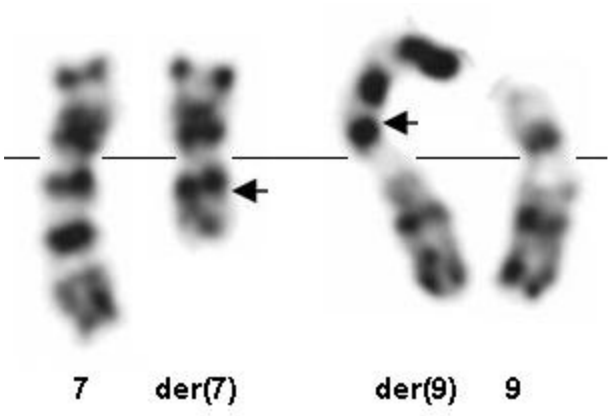


t(7;9)(q11;p13) RHG-banding (Courtesy Nicole Dastugue).

Clinics and pathology

Disease

B-cell acute lymphoblastic leukemia (B-ALL).

Phenotype / cell stem origin

Pre-B3 phenotype (CD10+ Cmu+) and pre-B2 phenotype (CD10+ Cmu-).

Embryonic origin

Only two cases described: a 38-year-old male patient and a 16-year-old male patient.

Treatment

GRAAL 2003 trial and LALA94 trial.

Evolution

Relapse post allograft for both patients.

Prognosis

Poor (16 months survival for both patients).

Cytogenetics

Probes

BAC probes: RP11-243F8 for PAX5 and CTD-2278A11 for ELN.

Additional anomalies

del(9)(p11p13) in 1 of 2 cases but without PAX5 deletion.

Genes involved and Proteins

PAX5

Location: 9p13

DNA / RNA

The PAX5 locus spans approximately 200 kb. PAX5 contains 10 exons and two distinct promoters resulting in two alternative 5' exons (1a and 1b). PAX5b is transcribed in the central nervous system and testis as well as in the B lymphoid lineage. PAX5a, also named B-cell specific activator protein (BSAP), is specifically transcribed in the B lymphoid lineage.

Protein

PAX5 is a member of the highly conserved paired box (PAX)-domain family of transcription factors. The PAX5 plays an important role in cell differentiation and in embryonic development. PAX5 is expressed from early stages of B-cell development up to mature B-cells and is down-regulated during terminal differentiation into plasma cells. PAX5 contains a paired box domain (DNA binding domain), a conserved octapeptide motif and a partial homeodomain. Its C-terminal region contains a transcriptional activation domain and the extreme C-terminal region acts as a repression domain.

ELN

Location: 7q11

DNA / RNA

ELN locus spans approximately 40 kb and contains 33 exons.

Protein

ELN is a 72-kDa insoluble extracellular matrix protein.

Results of the chromosomal anomaly

Hybrid gene

Description

5'PAX5-3'ELN, PAX5 exon 7 is fused in frame with ELN exon 2.

Transcript

The same PAX5-ELN transcript was amplified for both patients. Of note, the two alternative transcripts PAX5a-ELN and PAX5b-ELN were presents. The reciprocal ELN-PAX5 fusion transcript could not be amplified.

Detection protocole

The fusion transcript can be detected by RT-PCR using the 5' PAX5 sense primer: 5'-CCCTGTCCATTCCATCAAGTCCTG-3' and the 3' ELN antisense primer 5'-ATGAGGTCGTGAGTCAGGGGTC-3'.

Fusion protein

Description

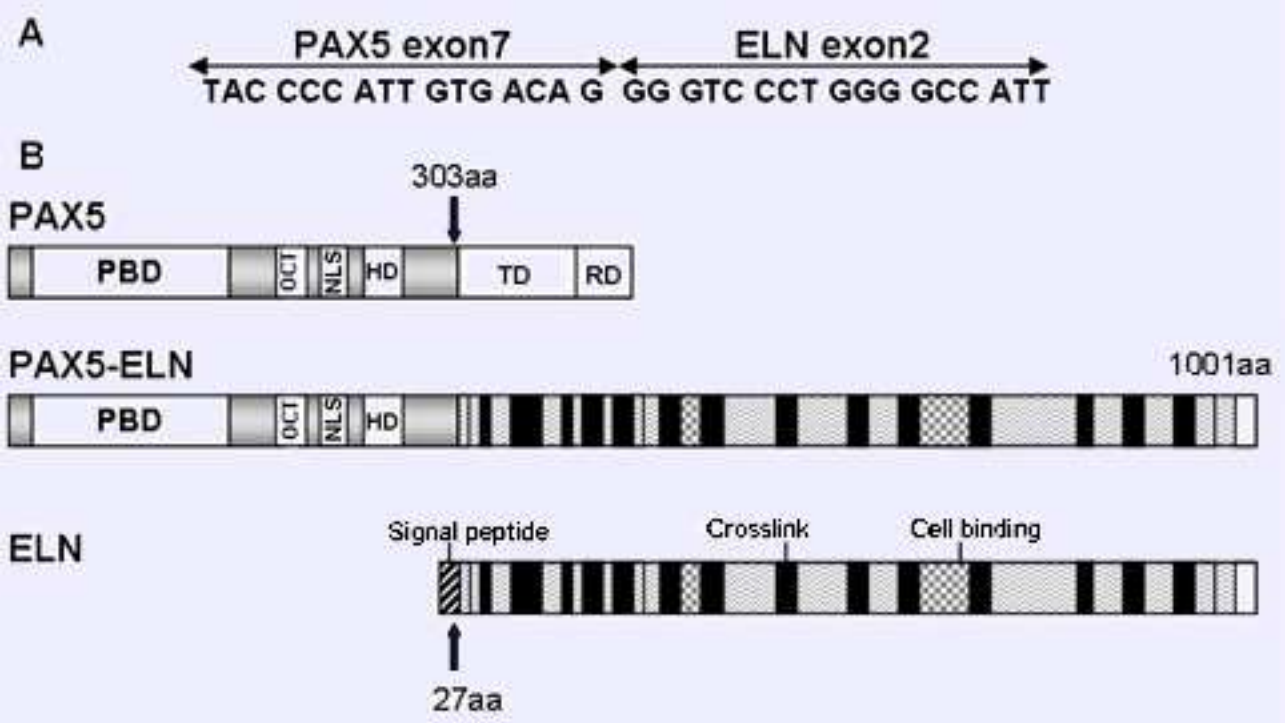
The PAX5-ELN fusion protein conserves the DNA binding domain of PAX5 and its NLS, but looses its transactivation and repression domain. The quasi entire sequence of ELN is preserved without its signal peptide.

Expression localisation

In HeLa cells transfected with the construction PAX5-ELN, the chimera is localized in the nucleus.

Oncogenesis

PAX5-ELN acts as a dominant negative on wild-type PAX5 in in vitro experiments that could explain the blockade of differentiation in leukemic cells.



Schematic representation of PAX5-ELN chimera. (A) Sequence of the in-frame fusion between exon 7 of PAX5 and exon 2 of ELN. (B) Structure of PAX5, PAX5-ELN and ELN proteins. PBD, Paired box domain; OCT, octapeptide; NLS, nuclear localization sequence; TD, transactivation domain; RD, repressor domain.

References

Bousquet M, Broccardo C, Quelen C, Meggetto F, Kuhlein E, Delsol G, Dastugue N Brousset P. A novel PAX5-ELN fusion protein identified in B-cell acute lymphoblastic leukemia acts as a dominant negative on wild-type PAX5. Blood 2007;109(8):3417-3423.

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